

New tools to select the right treatment: Using network meta-analysis to determine comparative efficacy of udder health products

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Abstract

We are fortunate to have several intramammary treatment products for clinical mastitis and dry-cow therapy available to us, but relatively few clinical trials compare these products head-to-head. Knowledge of relative efficacy of all available products is important for practitioners, where this information can be used to inform judicious antibiotic use. Network meta-analysis provides a method to synthesize evidence from all available trials and provide the relative efficacy of a network of treatments. This methodology is used extensively in human health and is becoming more common in animal health research.

Résumé

Nous avons la chance de disposer de plusieurs produits de traitement intramammaire pour la mammite clinique et pour la thérapie des vaches au tarissement. Toutefois, peu d'essais cliniques comparent ces produits entre eux. La connaissance de l'efficacité relative de tous les produits disponibles est importante pour les praticiens car cette information peut être utilisée pour permettre une utilisation judicieuse des antibiotiques. La méta-analyse en réseau fournit une méthode pour synthétiser l'évidence provenant de tous les essais disponibles et donne l'efficacité relative d'un ensemble de traitements. Cette méthodologie est très utilisée en santé humaine et est de plus en plus fréquente dans la recherche sur la santé animale.

Introduction

Mastitis is 1 of the most costly diseases of dairy cattle.⁵ In the United States, treatment for clinical mastitis represents the most common indication for antibiotic use in adult dairy cattle, with 16.4% of cows reported as treated in 2007, and cephalosporins was the most commonly selected drug class.¹⁴ While the bacterial etiology varies, a significant proportion of these cases benefit from prompt administration of an effective antibiotic, with or without other therapy. In the United States, more than 90% of dairy cows receive dry-cow therapy

after every lactation,¹⁵ with the goal of treating or preventing intramammary infections (IMI) during the dry period. Prepartum IMIs are strongly associated with risk of development of clinical mastitis in the first 2 weeks post-calving, which represents the highest risk period for this disease.⁴

Dairy farmers and veterinarians have a considerable number of antibiotic treatments available for prevention and treatment, including products of greater importance to human medicine. Veterinarians need information about the relative efficacy among products to facilitate their choices and, where possible, select efficacious products with the lowest human medical importance.

Determining Efficacy

There is a need for evidence-based antibiotic use protocols surrounding udder health.¹² However, randomized controlled trials often evaluate only a pair-wise comparison of products. Knowing the comparative efficacy of products of all treatment options would be useful for both producers and veterinarians. This information would allow efficacy to be weighed along with other decision-making parameters, including importance of the antibiotic to human medicine. Choosing ineffective antibiotics, or using antibiotics unnecessarily, contributes to antimicrobial use without benefit to disease control, impacting both profitability and animal welfare.⁸ Establishing relative efficacy of treatment options will serve to improve decision makers' ability to engage in effective stewardship of antibiotics through the strategic use of these products with knowledge of implications for animal health and welfare.

Knowledge Synthesis

Replication of results among studies is essential to draw overall conclusions about the effects of treatments and is a fundamental aspect of science. Systematic reviews of randomized controlled trials serve to synthesize information across multiple trials to yield a high level of evidence for efficacy of treatment under field conditions.¹³ Systematic reviews use evidence-based methods to identify, evaluate, and summarize

evidence for a specific research question,¹³ providing a concise, transparent overview of primary research for decision makers in one source.^{6,7}

Traditionally, if sufficient numbers of primary studies on a given comparison are available, a pairwise meta-analysis would be used to provide the relative efficacy of the 2 treatments (e.g. antibiotic A compared to antibiotic B). However, direct comparisons of potentially comparable interventions may be limited,¹¹ and especially when many treatment options are available for lactating or dry-cow therapy, a trial that includes all possible intervention options is not feasible. Pairwise meta-analysis, therefore, only provides information about a single comparison and does not provide a summary of evidence across multiple interventions.¹

Network Meta-analysis

A robust alternative is to conduct a network meta-analysis that combines all of the information from multiple trials and enables accurate and valid comparisons to be made for all available treatments. Network meta-analysis provides a method of assessing relative efficacy among many treatments by use of direct (studies which compare given treatments) and indirect (studies which share common comparators) evidence, and is a commonly used approach in human medicine.¹ The statistical methods for this approach are well established³ and have been used extensively in human health² and have more recently been adopted in animal health research.^{9,10}

For example, if we have trials that compare antibiotic A to antibiotic B, and others which compare antibiotic A to antibiotic C, we can know how B and C compare through their relationship with A (Figure 1). Trials must have at least 1 treatment common to the network; for example, in Figure 2, we have trials examining D compared to E, but no trials comparing either product to A, B, or C. In this case, we can know the relative efficacy of A, B, and C, and then separately, the relative efficacy of D and E, but no conclusions can be made comparing between the 2 networks of evidence. Alternatively, in Figure 3, now we have at least 1 trial comparing B to D, creating 1 larger network. In this case, we can establish relative efficacy among all products. Here we have direct comparisons among all products. Here we have direct comparisons between A-B, A-C, B-D, and D-E, but we also have indirect pathways of evidence, for example, between A

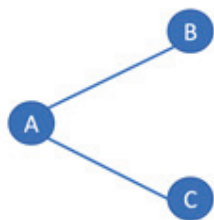


Figure 1. An example of a network of studies where there are direct comparisons between A and B, and A and C.

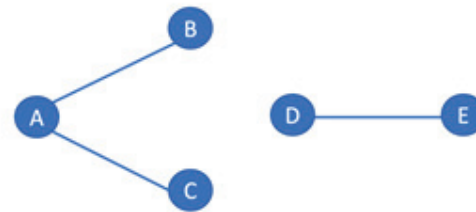


Figure 2. An example of a network of studies where there are direct comparisons between A and B, A and C, and D and E.

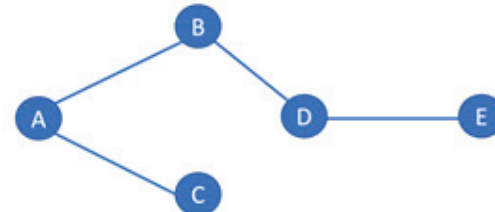


Figure 3. An example of a network of studies where there are direct comparisons between A and B, A and C, B and D, and D and E.

and D (through B), or A and E (through A-B-D-E).

An example of a larger treatment network plot is shown in Figure 4, with each red node representing a unique treatment. The size of nodes reflects the number of trials that included that treatment. Lines between nodes show the direct evidence in the network and reflect trials that compare the 2 treatments they connect. The width of the line reflects the total population size for the comparison.

There are several different outputs from network meta-analysis, but perhaps the most clinically meaningful one is the ranking plot. This is based on a Bayesian analysis where the risk of the outcome is calculated for each treatment over

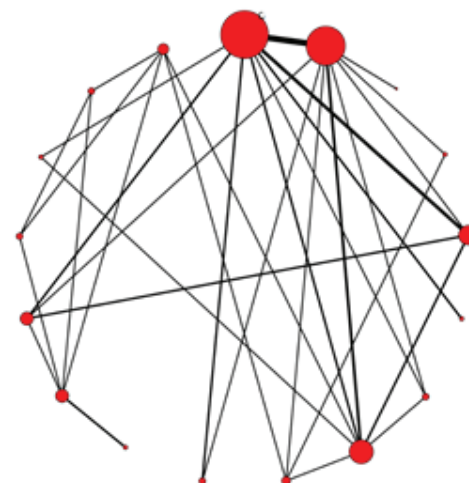


Figure 4. An example of a larger network, where each red node represents a unique treatment, and lines reflect direct comparisons between the 2 connected products. The size of the node reflects the number of studies with the specific treatment, and the width of the lines reflects the total population in that comparison.

thousands of simulations using a Markov chain Monte Carlo method. The ranking plot provides the mean ranking of the treatment and a 95% credibility interval. The example in Figure 5 shows the mean rankings of products A to I, with corresponding credibility intervals. In this proposed example, a better ranking (closer to 1) corresponds with a higher risk of a positive outcome (e.g. bacteriologic cure). In this example, treatments A, B, E, and F appear to be better than treatment C, but not substantially different between each other.

Conclusions

Systematic reviews incorporating network meta-analysis can provide practitioners and other decision-makers with a concise summary of the relative efficacy of multiple interventions for a given outcome. Knowledge of efficacy is essential for judicious antibiotic use, as a similarly performing product of lesser importance to human health could be chosen and use of ineffective antibiotics can be discouraged.

Acknowledgement

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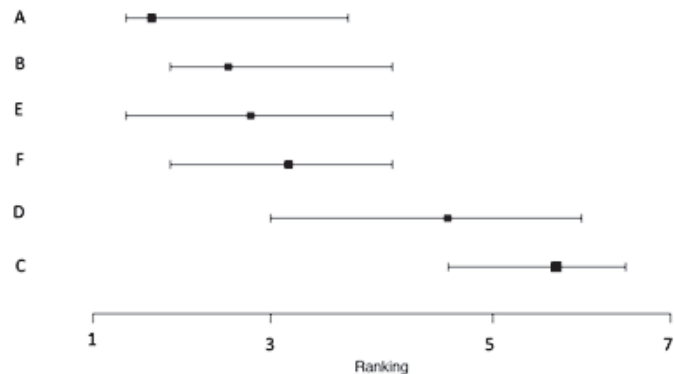


Figure 5. An example of a ranking plot, showing the mean ranking and 95% credibility interval for each treatment. In this example, a better (lower numbered) ranking reflects a greater risk of a positive outcome (e.g. bacteriologic cure).

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